

## Sugar-Coated Proteins Pave the Way to Improving Pancreatic Cancer Diagnosis



Pancreatic ductal adenocarcinoma (PDAC) is a deadly malignancy with an overall 5-year survival rate of 7%. By contrast, stage IA PDAC is associated with a 5-year survival rate of 40% after resection, underscoring the benefits of early diagnosis in conjunction with surgical intervention. Unfortunately, the vast majority of patients do not present with early PDAC, and approximately 80% of patients have metastatic or locally advanced cancer at clinical presentation, which preclude the possibility of curative resection. Key reasons for the late diagnosis of PDAC include the absence of symptoms or the presence of only vague symptoms in early disease, difficulties inherent in diagnostic imaging of the pancreas, and the absence of sensitive and specific diagnostic markers in the circulation.

Serum carbohydrate antigen 19-9 (CA19-9) is the only PDAC serum biomarker approved for clinical use by the Food and Drug Administration. CA19-9 is a glycan, and more specifically a sialylated lacto-N-fucopentaose II glycan that is related to the Lewis (a) antigen. Glycans are polysaccharides that attach to glycoproteins and glycolipids. O-linked glycans are attached to serine and threonine residues through O-linked N-acetylgalactosamine, and are abundant in mucins, whereas N-linked glycans are attached to the amide group of asparagine residues in proteins. Cancer can be associated with aberrant glycan structure and glycosylation that can, in turn, lead to altered function and generation of cancer-specific epitopes that can be useful diagnostically. Although antibodies against CA19-9 generally recognize the sialyl-Lewis A (sLeA) antigen, which may be expressed at high levels in PDAC, this marker lacks both sensitivity and specificity; is not expressed in approximately 14% of the general population, is not increased in approximately 25% of patients with PDAC, and serum CA19-9 level may be increased in patients with hyperbilirubinemia without PDAC.

In the article by Tang et al<sup>1</sup> in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, the investigators profiled the levels of multiple glycans and mucin glycoforms in plasma from 200 subjects with either PDAC or benign pancreatic disease, and validated selected findings in subsequent cohorts totaling 216 subjects. They found significant increases in glycans that are distinct from sLeA. Because glycans are carried by glycoproteins, and CA19-9 is carried by a variety of glycoproteins, including MUC5AC and MUC1, Tang et al<sup>1</sup> examined MUC5AC glycoforms and determined that in addition to sLeA, MUC5AC carried sialyl-Lewis X, a previously described isomer of sLeA, and sialyl-LacNAc type 1. They also assessed sulfated and sialylated variants of sLeA/sLeX. Impressively, the serum levels each of the other glycans performed as well as sLeA levels when

used as individual markers and were increased in distinct groups of patients. Moreover, the 3-marker panel provided 85% sensitivity and 90% specificity in the combined discovery and validation cohorts, by contrast to 54% sensitivity and 86% specificity for sLeA. The same 3-marker panel also yielded 80% sensitivity and 84% specificity in the independent test cohort. It remains to be determined whether the 3-marker panel also will be useful for monitoring PDAC recurrence and patient prognosis.

Each of these glycan markers was increased in some PDAC patients but not in others, leading Tang et al<sup>1</sup> to suggest that in addition to the utility of the 3-marker panel for improving the diagnosis of PDAC, comparison of sLeA-related glycans with CA19-9 could facilitate PDAC subclassification. It also is possible that this subclassification represents a broader approach than measuring individual proteins. For example, proteins such as CD44 and MUC1 carry sLeA glycans, and proteins such as Kras, SPARC, and Wnt7b express Lewis X glycans.<sup>2</sup> Although all of these proteins have been implicated in PDAC, glycan-based subclassification may offer greater power than analysis of individual proteins. In addition, some heparan sulfate proteoglycans are expressed aberrantly in PDAC, and the heparan sulfate proteoglycan glypican-1 has been shown to contribute to PDAC progression in a genetically engineered mouse model of PDAC.<sup>3</sup> Thus, glycan-coated proteins clearly have an important role in PDAC pathobiology, and the current findings underscore the importance of advancing our knowledge of the role of glycans in PDAC. Of course, further study is required to determine whether glycan-based subclassification is useful. Nonetheless, these and other data show that tools such as genomics, epigenomics, proteomics, metabolomics, and glycomics are important for profiling cancers. The present findings also raise the possibility that the expression of specific glycans within the pancreatic tumor mass, their presence in serum, and their possible ability to circulate within exosomes, especially given the known presence of CA19-9 in exosomes and the potential of PDAC-released exosomes to facilitate distal metastases, could help guide precision medicine strategies that maximize therapeutic benefits in PDAC.

MURRAY KORC, MD

Department of Medicine, Biochemistry  
and Molecular Biology  
Indiana University School of Medicine  
Indianapolis, Indiana

Melvin and Bren Simon Cancer Center  
Pancreatic Cancer Signature Center  
Indianapolis, Indiana

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### Correspondence

Address correspondence to: Murray Korc, MD, Indiana University Simon Cancer Center, Indiana University School of Medicine, 980 West Walnut Street, Walther Hall, Room C528, Indianapolis, Indiana 46202. e-mail: [mkorc@iu.edu](mailto:mkorc@iu.edu).

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